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ON THE ETIOLOGY AND SYMPTOMATOLOGY OF GOITRE.*

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The persistent and recognisable enlargements of the thyroid gland which we classify under the name of Goitre or Bronchocele, are from almost every aspect a pain to the pathologist, even if like so many human ills to so many patients, an interesting pain. He knows not their cause: when he comes to study them histologically, the changes they present are bewildering in their manifoldness: his medical and surgical colleagues have provided him—perhaps it would be more courteous, if not more correct, to say, can provide him—with singularly few data whereby to recognise different forms of disease associated with different anatomical lesions, and so to establish a useful classification; while when symptoms are present the explanations he can offer as to the mode of development of the same, are such that he has found it hard even to convince himself that they are correct. If he ascribes them directly to the local enlargement of the organ, he can in the majority of cases find no absolute relationship between the size of the goitre and the extent of the symptoms, if to aberrant or excessive action of the gland, then again he can make out no sure relationship of the size and rate of growth of the goitre to the extent of the symptoms; while, if he looks beyond the gland to some constitutional disturbance leading at the same time to the goitrous enlargement and to these other symptoms, he finds himself in the *impasse* of not being able to state with any certainty what that constitutional disturbance can be.

Yet this very fact that he is so painfully ignorant about the subject does, it must be confessed, stimulate curiosity. Indeed, an obscure disease is to the pathologist what a virgin peak is to the mountaineer, and medical men will continue to attempt to solve the problem of the causation of such obscure diseases with untiring zest until the labours of many lead to some one finding the solution. To-day we shall not scale the peak: I can but point out to you what would seem the right path to take in order to reach the summit, and, cutting a few steps at the bottom of the ascent, may make that ascent a little more possible, a little less toilsome.

Here in connection with the *causation* of goitre the theories that have been suggested are legion: merely to enumerate them would far more than take up all the time at my disposal this morning. In Swit-

* Delivered at the Cooke County Medical Hospital, Chicago, Nov. 29th, 1899.

zerland and England it used to be popular to explain goitre as due to some subtle influence brought about by life in mountainous regions, but our Island of Montreal can scarcely be spoken of as anything but a rich alluvial plain with one old volcano very much the worse for wear cropping out of one small portion thereof. And yet the district is so goitrous that in some of the French-Canadian villages but a few miles from Montreal, scarce a family is to be found that has not one or more goitrous members. Then, too, the carrying of loads upon the head has been called a cause, but rural Montrealers do not carry loads on their heads, nor do animals do this—horses and dogs; yet they are found similarly affected.

Again, the geographical conformation of the country has been regarded by many as explaining the relative frequency of the condition. Bircher has especially upheld this geological theory, if I may so term it, of goitre. In Switzerland, for example, he has pointed out that goitre is almost limited to Silurian and Devonian formations and to the Carboniferous and Permian deposits; Johannessen has reached practically the same conclusion in Norway. In England Berry finds goitre only where there are chalk and sandstones of Triassic development, while it is absent where there are eruptive rocks. Bircher comes to the conclusion that goitre only occurs where there are deposits, more especially marine deposits, of the palæozoic age; whereas where the rocks have been modified by internal heat and where the various deposits are of fresh water origin, there is absence of the condition.

There is a wide field for more thorough study of the geological incidence of goitre upon this continent. It is certainly remarkable, looking at a geological map of Canada, to see how the main goitre areas conform to the Silurian and Devonian deposits. From the peninsula of Ontario right down to Quebec the St. Lawrence valley on either side is mainly Silurian, the limestone deposits being only broken at the Thousand Islands, where a band of older Laurentian rock cuts across.

Further information is required as to whether goitre occurs in the Laurentians to the north (which, while of fresh water origin, are greatly modified by heat). In discussing with Dr. Adams, our Professor in Geology, and pointing out to him that according to my colleague, Dr. Springle, cases of goitre are occasionally met with occurring along the north bank of the St. Lawrence, even as far as Labrador,* he called my attention to the fact that occasional deposits of limestone were to be found here and there throughout that extensive Laurentian area, from Quebec onward towards the sea, and that notoriously wherever the limestone is present the districts are more fertile and there especially people tend to settle. Hence, if we do come across occasional goitre in the

* Vide Dr. Springle's article in the last number of this JOURNAL, p. 909.

Laurentian area, very careful study has to be made of the deposits before it can be definitely stated that the disease occurs in areas purely Laurentian or over these later rocks. Thus there is an interesting opening for individual or collective investigation with regard to the distribution of the disease upon this continent, special attention being given to the geological formations over which the condition is frequent. Certainly with regard to Bircher's work, Kocher has brought forward evidence to show that his results are not wholly correct.

That the water habitually drunk has to do with the development of goitre is generally accepted, but *what* it has to do is still a matter of very considerable, nay, absolute, doubt. Certain wells, so-called goitre wells, appear especially to afford water, which, when drunk leads to enlargement of the thyroid and typical goitre. To the existence of these wells the Swiss more especially have called attention, and Kocher is a strong adherent of this connection between the water drunk and the development of the condition. Bircher gives an example of a village in the Aarau, Switzerland, which was at one time markedly goitrous, and which in 1884 put in waterworks, obtaining its water from a goitre-free region on the other side of the river Aar. As a result, the percentage of cases of goitre among the school children in the village, diminished as follows:

In 1885, 58% affected	In 1886, 44% affected
In 1889, 25% affected	In 1895, 11% affected

Other examples almost as strong as this can be collected showing the relationship between the drinking water and endemic goitre.

As to what in the water leads to the disease, observations have so far led to negative results. The presence of chalk and magnesia has often been suggested, but numerous wells and waters rich in chalk and magnesia are found unassociated with goitre, and some of these, indeed, are found when drunk to be beneficial and to be associatel with diminution in the size of the enlargement. Several notorious goitre wells are completely free from these substances. The same is true with regard to waters containing sulphate of iron and copper, while feeding animals with various salts and metals has never been found to lead to the development of the condition. Of minerals, iodine has more especially of late years been suggested as associated with the condition, for Baumann's observations have shown the remarkable iodine-containing body present normally in the colloid substance of the thyroid. But even with iodine, there are several valleys and regions where the water is rich in it and yet goitre does not occur, and contrariwise iodine free springs are more common throughout the world than those containing iodine, and the majority of such springs are unassociated with the development of goitre. In fact, every individual chemical constituent of the water would seem to have been at one time or another studied and suggested as of possible etiological moment in this disease, and every one in turn upon

further study has been found to have no relationship. This being the case, we are thrown back upon the possible existence in the water of some living organism.

Can we regard ordinary goitre as being of infective origin? In favor of such a theory not a few facts have been brought forward. Notably there is in addition to its curiously endemic nature, the infrequent but well-established occurrence of a sudden development of the condition in an epidemic form in large bodies of men, troops, etc. Thus Valentin recorded an instance in an infantry regiment which had for 5 years been established at Caen, and then went to Nancy. Here goitre had never been endemic and sporadic cases were rare. The regiment was for some little time at Besançon, and there only had come into contact with goitrous individuals. Within a few months no less than 38 members of the regiment showed goitre. During the next four years the number increased, 205 in 1784, 425 in 1785, and so on until altogether 1,009 soldiers of the regiment were affected, while the other troops in garrison there, with the exception of an occasional case in one cavalry regiment, showed no cases. It is remarkable that here the officers who were in the same barracks and who drank the same water, were not affected. Similarly at Belfort, in 1877, out of a garrison of 5,300 men, there were no less than 900 acute cases of the disease. At Silberberg in Silesia, Haneke recorded, in 1820, the appearance of goitre in the garrison, and in the course of one year in a newly recruited battalion of 380 men, 310 presented the disease. Hirsch, A. von Humboldt and Virchow, all careful and thoughtful observers, years ago held that something of a miasmatic nature must lead to the development of the condition.

Some of the most remarkable observations upon this infectiousness of water were carried out by Lustig and Carle, who selected a horse and some dogs from a goitre-free region, kept them in another goitre-free region and gave them exclusively water from a "goitre well" to drink, The horse after some weeks showed definite enlargement of one lobe of the thyroid, and when this was extirpated, the other lobe enlarged, the enlargement diminishing when other water was supplied. So also with the dogs: 10 were given filtered and boiled goitre well water and remained free from goitre; 13 were given unfiltered water, and one at least showed a well-marked enlargement of the gland. Further, a goitrous dog taken from a goitre region, part of whose thyroid was extirpated anad showed characteristic changes, presented a marked reduction of its goitre to normal size when given filtered goitre well water to drink.

These experiments can at most be said to be suggestive; the number is insufficient for us to regard them as at all absolute. Nor when we come to examine the numerous records of bacteriological examination

of these goitre waters do we arrive at anything but what is most unsatisfactory. Lustig and Carle, it is true, indicate a bacillus which liquefies gelatin and which has been constantly present in the goitre waters examined by them. Kocher points out that the goitre waters are distinguishable from the non-goitrous in Switzerland by the relative abundance of bacteria in them. Klebs found certain infusoria; Bircher a diatom together with polymorphous bacteria; while Waters recently has suggested that certain amœbæ are present therein, upholding a theory somewhat similar to the present rather popular sporozoon theory of cancer and malignant growths.

This mere recapitulation of unconfirmed observations shows that this bacterial or miasmatic theory remains to-day as it was 30 years ago—still a theory without any positive fact whereby to establish it. The most that we can say is that there is obviously some relationship between the water drunk and the development of the disease and that a microbic causation is well within the bounds of possibility. But even if we grant that there is this possibility, it presupposes either that we are dealing with the entrance into the system of some toxic substance, produced by microbes in the alimentary canal and especially acting upon the thyroid tissue, or with infection proper. If there be infection, then it must be rather a remarkable character, for in the first place, the condition only shows itself in the majority of cases from the age of 8 years onwards, and in the second place if the individual be removed from a goitrous region sufficiently soon after the development of the disease and before chronic and cystic changes have ensued in the gland, then the tendency is for the enlargement to disappear. In other words, the infection if present must depend largely upon local conditions and does not tend to be progressive or self-propagating. We have, that is to say, to recognise a novel form of latent infection, if I may so term it; we have to suppose that so long as the individual remains in a goitrous region infection continues, and that the goitre is an indication of an imperfect neutralisation of the germs and their products: once the individual leaves the region, there being no longer infection, the destruction of the germ is complete and the thyroid eventually returns to a condition of equilibrium. Such latent or subinfection is possible, but in the absence of any positive evidence of the existence of any specific microbe, we have no right to base any theory upon its possibility.

Of more real and practical interest at the present moment is the *symptomatology* of goitre. Only recently is this becoming at all carefully studied, and the study, it has to be confessed, shows what at first sight appears to be a most contradictory series of disturbances. For on the one hand we not infrequently come across in the post mortem room, small goitrous enlargements of the thyroid, unrecognisable during life,

and judging from the clinical history, absolutely unassociated with any symptoms, and the same is true of nodular goitres of fair size and causing a definite disfigurement in the neck. On the other hand, there may be very various symptoms present, and the puzzle is that at times symptoms referable to excessive production of thyroid secretion occur simultaneously with others which it is certain we should attribute to defective discharge of this secretion. Let me here attempt to recount and classify the main symptoms which have been observed :—

There are certain definite symptoms which may with certainty be ascribed to *Pressure*. From its position the thyroid when enlarged is liable to disturb the function of several important organs: the trachea, the œsophagus, the arteries and veins of the neck, and several nerves, as for example, the superior laryngeal (rarely), the inferior laryngeal, the posterior auricular, the vagus, the sympathetic, the cardiac roots of the sympathetic, the accessorius, the cervical plexus, facial nerve, and the brachial plexus. Without taking into consideration the possible results of pressure upon all of these, we know with certainty that there may be grave pressure upon the trachea leading to dyspnœa and other respiratory disturbances; this pressure is generally lateral, but may be also from in front.

Even relatively small goitrous enlargements, if projecting backwards, may cause severe dyspnœa, and apart from mere dyspnœa, we frequently find distinct alteration in the voice, a rawness and want of tone. This may in part be due to compression upon the trachea, but Wölfler found more or less paralysis of the vocal cords in 10 per cent. of the cases he examined; Krönlein out of 191 subjects found 62 having a history of paroxysmal dyspnœa and 49 showing a definite disturbance of the voice; 7 of these 49, whom alone he was able to examine laryngoscopically, showed unilateral paralysis of the cords. Such paralysis is evidently due to direct pressure upon the recurrent laryngeal.

Pain behind the ear, which not infrequently occurs, has been ascribed to pressure upon the posterior auricular nerve; cramp in the neck muscles would seem to be due to pressure upon the accessorius; the compression of the large veins leads to congestion of the same and a certain amount of swelling of the neck and cyanosis of the face, while occasionally, though not as frequently as might be expected, there is a certain amount of dysphagia; where this is the case there is not infrequently enlargement of accessory lobes between the trachea and the œsophagus.

All these symptoms mentioned so far may with safety be ascribed to pressure and to pressure alone, but they far from exhaust the symptoms which may be noted. Frequently there are psychical disturbances. My own experience—and here I speak under correction—is that those having large and generalised goitres are in general dull, torpid, of low mental powers, not to say tending towards mental failure, and in addi-

tion they often show a rather special physiognomy, heavy, expressionless, and recalling strongly the appearances met with in those suffering from myxœdema. In this connection it may be called to mind that whereas sporadic cretinism is in general associated with atrophy and absence of the thyroid, where cretinism is endemic, over 50 per cent. of the cretins are goitrous—and cretinism is infantile myxœdema.

But, on the other hand, we have another series of cases in which the psychical disturbances, contrariwise, are those of mental irritation: at patients are highly nervous, sleepless, possessing a fear of impending trouble and unable to settle down to sustained work—symptoms, in short, closely resembling those found in exophthalmic goitre, and what is more interesting, when nodular goitrous masses are removed, as Dr. Shepherd* has noted, the symptoms rapidly disappear. They seem, in short, to be allied to what one finds in hyperthyroidism and in exophthalmic goitre or Graves' disease.

It is now some years since Dr. Shepherd called my attention to the existence of nervous and psychic disturbances which he had observed in several of the goitrous patients who had come under him for operation. It was impossible from his description to fail to recognise that these were of the same nature as those manifested in Graves' disease. Nor has this similarity escaped attention abroad. In France, Joffroy and Achard (*Arch. d. Med. Exper.* 5, p. 824, 1893) were among the first to call attention to this relationship, and have gone so far as to state that from an anatomical point of view there is nothing by which one can distinguish a simple goitre from the goitre of Graves' disease. (Though here I disagree with them.) They call attention to the frequency with which one sees the symptoms of Graves' disease developing in subjects who show a goitre of more or less old standing and of endemic origin. Clinical examination, on the one hand, does not permit the establishment of a radical separation between these so-called false exophthalmic goitres and the classic Graves' disease. Nor, again, therapeutically can any distinction be made, inasmuch as certain cases of Graves' disease are like ordinary goitre, aided by operative treatment. With Möbius they include the false exophthalmic goitre, so-called, along with true Graves' disease; for in Germany Möbius had already called attention to this relationship, and in a later article in Nothnagel's Specielle Pathologie, 1896, he dwells very strongly upon this same point. He divides the cases of exophthalmic goitre into, *primary*, in which the goitre and other symptoms of disease appear together; and *secondary*, in which the symptoms supervene upon an old ordinary goitre, and these secondary he regards as the more common, only differing otherwise from the primary in being usually of a more chronic nature and incomplete in the

* Vide his address in last month's number of this JOURNAL.

number of the symptoms shown. In these secondary cases we have everything from the mere simple case of goitre accompanied by palpitation and paroxysmal tachycardia, to goitre with palpitation and tremors, and to fully developed Graves' disease with persistent tachycardia, tremors, exophthalmos, Stellwag's sign, pigmentation, etc. More often in these secondary cases, from the large size of the goitre, there may occur definite symptoms which can only be referred to pressure, symptoms not necessarily present in the primary form.

It has been the custom to regard ordinary goitre and exophthalmic goitre or Graves' disease as two absolutely distinct and widely separate conditions. The symptoms of the former, when they have approximated to the latter, have been mainly ascribed to local pressure in the neck and have been disregarded by the majority of medical men. The extreme care with which the symptomatology of exophthalmic goitre has been studied in England, France and Germany, as again on this continent, and the remarkable concatenation of diverse symptoms that has been made out :—tachycardia, exophthalmos, Stellwag's sign, von Graefe's sign, Möbius symptom (insufficiency of convergence), tremors, pigmentation of skin, paroxysmal diarrhœa, sleeplessness, mental irritability and other psychical disturbances, have almost inevitably led to this condition being regarded as a disease apart. Here I do not wish to indicate that the causation of the two conditions is identical, for my opinion is that the causation is absolutely different, but I do wish to emphasise the fact that the sharp limitation which is usually held to obtain between ordinary and exophthalmic goitre, is often non-existent, and that the one condition not infrequently is accompanied to a greater or less extent, by symptoms of the other.

What, then, are these symptoms which are allied to those seen in exophthalmic goitre ? As already stated, there are the psychical disturbances—nervousness, fearfulness, inability to take up sustained work and sleeplessness. Tremors, it is true, have rarely been noted, but this is possibly because no one has made the same careful search for them that Marie did for the existence of tremors in Graves' disease. Another very characteristic and not infrequent disturbance is paroxysmal dyspnœa, which is easily mistaken for asthma. These paroxysms have in general been ascribed to the catarrhal condition of the mucosa secondary to the pressure. Two sessions ago I brought before our Medico-Chirurgical Society in Montreal, a thyroid from a case in which the main feature was this history of paroxysmal dyspnœa mistaken for asthma. It was a case in which we found at post mortem enlargement purely of the middle lobe of the organ, scarcely recognisable in the stout neck, and which, while undoubtedly pressing upon the trachea, had not caused sufficient narrowing to satisfactorily explain the dyspnœic condition. At that time I suggested that the sudden vascular enlarge-

ment of this highly vascular lobe might give the adequate explanation. Dr. Shepherd has verbally reported to me a recent case of his in which operation upon a patient suffering from extreme dyspnœa of sudden onset revealed similarly an enlarged very vascular middle lobe, in which hæmorrhage had occurred, and had caused the same symptoms. But further study has convinced me that this explanation does not suffice for all cases. Some, like Lücke, doubt as to whether there is not here some central nervous disturbance also present. Something beyond mere pressure appears to cause the attacks—a something either of nervous or toxic origin. For these attacks frequently manifest themselves in the middle of the night and under conditions in which it is difficult to imagine any cause for the sudden enlargement.

It has to be kept in mind that just as in exophthalmic goitre, so here there may be characteristic heart troubles. We owe to Kraus the most recent study of the goitre heart. While he denies the relationship between the ordinary and exophthalmic goitre, he nevertheless points out very clearly that in the cardio-vascular disturbance of ordinary goitre, tachycardia is the most important symptom. According to him, the symptoms have two stages of intensity : 1st, increased action, more rapid pulse, with or without palpitation, the rate varying between 90 and 120, and occasionally becoming as rapid as 140 per minute. With this increase there is also a stronger beat of the heart, a heaving apex beat, a visible pulse, particularly in the carotids; in the radials this is large and rather soft and of a dicrotic character. The second group of cases of greater intensity occurs in long standing conditions or after repeated exacerbations, and now one has every evidence of dilatation of the heart, especially of the left side. Such cases at post mortem show sometimes no special hypertrophy of the organ, but in others there is a true hypertrophy. This, according to Kraus, is relatively frequent, and has associated with it a degeneration of the myocardium. Kraus' observations are based upon a long continued study of 15 cases of the disease; he calls attention to certain observations of Cyon, which show that removal of the thyroid gland leads to conditions in the organism which stimulate directly the nerve system and especially affect the sympathetic ganglia and the accelerator fibres of the heart. On the other hand, iodothyrin stimulates more the regulator or inhibitory apparatus of the heart and vessels. In the goitre heart, according to Kraus, one notices both these occurrences, namely, increased rapidity of the pulse and strengthening of the heart beat, and he concludes that in goitrous patients there is, through some disturbance of the gland, the simultaneous increased stimulation both of the accelerator and of the inhibitory nerve fibres of the heart, and that mere increase in thyroid secretion will not explain these.

But clearly the tachycardia and other vascular disturbances generally absent, or when present transient and of a moderate degree, seen in cases of ordinary goitre, are not merely those of pressure, and herein they correspond with the similar though more extensive changes seen in exophthalmic goitre.

Further, it has to be kept in mind that there may be a certain amount of exophthalmos in a case of ordinary goitre. Sometimes it is unilateral, and this unilateral development is perhaps best explicable by presupposing some pressure upon the sympathetic on that side. It is, however, doubtful whether exophthalmos is to be ascribed merely to irritation of the sympathetic nerves. Indeed, Askanazy's most interesting study upon the condition of the muscular system in Graves' disease shows the development of marked degeneration of the muscles during its course,—fatty degeneration and fatty infiltration—which explain the tremors, the imperfect expansion of the chest (Bryson's sign), the imperfect convergence of the eyes (Möbius' symptom), and to a large extent, the exophthalmos.*

The above recital shows remarkably the very suggestive relationship between ordinary goitre and exophthalmic goitre; indeed, the one may pass imperceptibly into the other.

Yet before we can proceed to attempt to draw any conclusions with regard to the relationship between ordinary and exophthalmic goitre, there is yet another class of cases that is to be considered—that class which French writers have referred to as "Formes Frustes"—incomplete forms. On this continent it is Dr. W. H. Thomson, of New York, who has most persistently drawn attention to the existence of this class of cases, a class characterised by presenting to a greater or less degree the remarkable symptom-complex of exophthalmic goitre, without however any primary evidence of enlarged thyroid,—exophthalmic goitre without exophthalmos, and without goitre. These cases show the tremors, the wandering pains in the extremities, behind the ear and in the muscles and elsewhere, accompanied by more or less hyperæmia, often noted in exophthalmic goitre; they have most characteristically a condition of persistent tachycardia, the pulse varying from 90 to 120, while a further prominent symptom, equally a feature of exophthalmic goitre, is the occurrence of paroxysmal diarrhœa, diarrhœa coming on suddenly with no apparent cause, and disappearing with equal suddenness. Indeed, in most cases the first symptoms recognised are in association with the digestive tract. But these patients have neither goitre nor exophthalmos at first, although with the persistence of this condition for some weeks or months enlargement of the thyroid tends to supervene and sooner or later a definite condition of exophthalmos with von Graefe and Stellwag's signs tends to show itself. I have come

* Vide extract in this JOURNAL in May, 1899, p. 357.

across one such case. The symptom-complex is so remarkable, the pains present features differentiating them from muscular rheumatism on the one hand and from the ordinary neuroses on the other, so that the cases stand out as a very distinct group, the nearest approach to anything like them being met with in certain conditions of enteroptosis and wandering kidney, in which, again, the abdominal region of the disturbance is a prominent feature; and yet, as I say, it is only relatively late on in the condition that we obtain evidence of hypertrophy or other enlargement of the thyroid. That the thyroid has some relationship or is affected in this condition is shown by the fact that it is peculiarly liable eventually to undergo enlargement. The condition, in short, tends to develop into unmistakable exophthalmic goitre, and that being the case, I cannot but agree with Dr. Thomson that we have to include this series of cases in any consideration of the etiology of Graves' disease. But doing this, it is obvious that we are forced to see that thyroid enlargement is not to be considered as the essential primary feature in the latter condition. The more we consider the matter, the more obvious it is that no organ in the body, unless it be the seat of aberrant new formation, causelessly undergoes enlargement. Even when there is such aberrant new formation we are now more and more recognising that some stimulus must be there to induce the hyperplasia. There is something behind the hyperactivity and hyperplasia of the gland causing their development, and we have to look beyond the thyroid for the cause of exophthalmic goitre, a cause by no means necessarily the same as that of ordinary goitre.

Before proceeding to this search it will be well to sum up the main conclusions reached thus far: these would seem to be :—

1. That the causation of ordinary endemic simple goitre is directly associated with the water habitually drunk by the subjects of the condition.

2. That no single constituent or contamination has so far, despite extensive search, been found common to the waters of goitrous districts.

3. That the peculiar epidemics at times recorded, coupled with this lack of discovery of chemical or toxic cause, appears to indicate miasmatic, *i.e.*, microbic causation.

4. That if it exists, the microbic agent is yet to be discovered.

5. A long series of forms can be made out from, on the one hand, those showing well marked goitres with dulling of intellect and bodily habit approaching to the myxœdematous type, through goitres presenting no generalised disturbance, save occasionally such as may be attributed merely to pressure upon the surrounding organs, to other forms of ordinary goitre showing symptoms of the same order as those seen in exophthalmic goitre, to cases of true exophthalmic goitre, and finally, to

cases showing no enlargement of the thyroid but certain of the general symptoms which are peculiar to Graves' disease.

It has to be confessed that so far these conclusions do not appear to hang very closely together, nor have we gained any thoroughly comprehensive view of the nature of goitre or of its relationship to Graves' disease—at most we recognise some obscure relationship between them, but at the same time we are forced to acknowledge that certain essential members of the Graves' symptom-complex can show themselves without any sign of thyroid enlargement.

Can we gain any further and surer basis for comprehending the relationship by a study of the anatomical changes found in these different conditions? I think we can, and in this study we find the key, if not to the whole problem, at least the key to the connection between these different forms of disease. It is now common knowledge that in myxœdema and cretinism we have conditions characterised by, nay, following upon, complete atrophy or loss of function of the thyroid, while, on the other hand, in typical Graves' disease, as Möbius suggested and Greenfield has clearly demonstrated, we have anatomical indication of the reverse, of hyperplasia of the thyroid tissue coupled with increased secretory activity. But the significance of the essential anatomical feature of the common goitre has not, I think, as yet been grasped. This common parenchymatous or colloid goitre is characterised by localised and lobular or by generalised distension of the follicles with dense colloid material. The individual follicles are greatly enlarged, so that the first impression given is one of actual overgrowth of the gland tissue. I will not say that such hyperplasia is not at times present, for I believe that it is, but this I will say, that in the main it is factitious and only apparent, the enlargement being due to a heaping-up of colloid material in the individual follicles,—a heaping-up so extensive that in enlarged glands we come across abundant evidence of a condition identical in nature to that observed in the emphysematous lung, namely, atrophy and absorption of the walls of adjacent follicles, so that large compound follicular cavities are developed. At the same time, the epithelium, instead of being cubical, or indeed of the lowly columnar type, as in the healthy gland, is flattened or even reduced to little beyond a string of nuclei, just as we find it in retention cysts. The histological appearance is not that of excessive activity of the glandular tissue, but, on the contrary, of obstructed function. In short, these goitres present every sign of retention and inspissation of the follicular contents.

We know further, by the observations of Hürthle and others, repeatedly confirmed of late years, that normally the contents of the vesicles find their way into the rich network of lymphatics surrounding the individual follicles, and it may be under certain conditions, into the almost as abundant network of the venous capillaries. For the thyroid

is an organ rich both in blood vessels and lymphatics and, as pointed out long ago by Wölfler, these stand in especial relationship to the follicles. Now, just as in the emphysematous lung, the distension of the air sacs leads to flattening of the capillaries and their walls, diminution in the lumen of these capillaries, increased friction and resistance to the blood flow, and as a consequence to continuing atrophy of the walls of the air sacs, accompanied by imperfect respiratory function, so in the thyroid, distension of the follicles must tend to obstruction of the surrounding lymph and blood vessels, and so must arrest the discharge of the colloid material. Or, to sum up, anatomically we have every indication that the *common colloid goitre is pre-eminently a condition not so much of hyperplasia and overgrowth of the specific thyroid tissue as of retention of the glandular secretion.* If this be the case, and the more I study material from such goitres, and the more I recall the appearances observed in material studied during the last few years, the more convinced I become of the correctness of this view, then it becomes possible to recognise the relationship between the different states already referred to. Briefly, we recognise the possible development of the following series of conditions :—

1. Disturbance of the thyroid so extensive as to lead to atrophy of the gland tissue, with the complete symptoms of *cretinism* (when occurring in the young), and of *myxœdema* (in the adult).

2. Disturbances (whether directly affecting the functional gland tissue or the paths by which the secretion of the same enters the general circulation) insufficient to cause destruction of the gland tissue, but leading to arrest of discharge of the specific secretion from the follicles and heaping up of the same throughout the whole organ :—*generalised colloid goitre with myxœdematous or cretinoid symptoms.*

3. Localised disturbance of the above nature, the remaining portions of the gland continuing to perform their functions normally :—*Nodular goitre with absence of general symptoms, but with possible symptoms due to pressure of the enlarged portions of the gland upon the surrounding organs.*

That a relative small portion of healthy thyroid can, after destruction of the rest of the gland, subserve the needs of the body, has been abundantly demonstrated by the observations of Halsted and others.

4. Localised disturbance leading to the heaping up and retention of colloid material in certain lobules of the thyroid, but with, in addition, the occasional occurrence of nervous stimulation or altered vascularity of the gland whereby increased absorption or discharge of the retained material into the circulation is favored: *Ordinary nodular goitre* with paroxysmal dyspnœa, paroxysmal tachycardia and other transient symptoms of hyperthyroidism or of Graves' disease.

If we are prepared to admit that the symptoms of exophthalmic goitre

are largely due to increased discharge of thyroid secretion into the general circulation, then these symptoms manifesting themselves now and again in the course of ordinary goitre are best to be explained by this supposition that the retained secretion by some one or other agency undergoes transient liberation causing thus a temporary excessive discharge of the secretory substance into the general circulation.

5. Supervention of increased discharge of thyroid secretion into the economy in a gland which is already the seat of ordinary retention goitre : *Secondary Graves' Disease, i.e.*, persistent tachycardia and other classical symptoms of Graves' disease following upon an ordinary goitre. As already stated, we are forced to recognise the frequency of this transition from ordinary to exophathalmic goitre. The occurrence, however does not imply that both conditions are due to one common cause. As a matter of fact, in regions where goitre is endemic, it is noticeable that we rarely come across well-marked examples of Graves' disease, so that we have almost a paradox that whereas so frequently in exophthalmic goitre we meet with the pre-existence of a nodular goitre, where goitre is endemic Graves' disease is relatively rare or not more common than elsewhere.

I have been not a little struck by the observation made to me by Dr. Springle, an observation which may possibly explain this apparent paradox. He has pointed out to me that whereas goitre is common immediately outside Montreal, in Montreal itself and in large towns and cities generally we rarely come across a fully developed goitre. Very possibly the water supply may be an explanation of this infrequency in Montreal itself. On the other hand, we do meet with cases of Graves' disease in this and other cities.

A case brought to my notice by Dr. Kinghorn, of Saranac Lake, N.Y., during this last winter appears to me rather suggestive. It was that of a young woman of 22, who since the age of 9 had had a recognisable goitre. Her mother was the subject of goitre from her early childhood, the goitre had become of great size after the birth of her second child, though later it had subsided until now all that is left is a mass the size of a hen's egg in the middle of the neck. One sister had been the subject of goitre at the age of 14, but it had subsided, and now it is not recognisable.

Until the age of 9 the goitre gave the patient no trouble; she noticed occasionally that it had increased in size, as do all goitres. At 19 she came in from the country, where she had previously lived in a very quiet place upon Lake Champlain, and became a waitress at a boarding-house in the little town of Saranac Lake.

The work was new to her, and, as she states, she was very nervous over it and very soon the goitre became large and nervousness more marked. She herself ascribed the nervousness and the goitrous enlarge-

ment to the change in her work. After a time she gave up working and returned home, when the goitre and all the symptoms subsided. Last winter she again came to Saranac Lake and went to help at her brother-in-law's store. This store is one of the largest in the little town, and further, had just been completely altered, so that she was very actively employed. Now again the goitre rapidly enlarged and palpitation came on, and when seen by Dr. Kinghorn she had definite symptoms of Graves' disease, tachycardia, exophthalmos, Stellwag and von Graefe's signs, palpitation and dyspnœa on exertion. The right lobe and the isthmus of the thyroid were principally enlarged. In addition, she had been liable to vomit, the vomiting coming on suddenly after each meal.

May not the more active life of the dweller in a city in part prevent the development of ordinary goitre, and, on the other hand, may not increased nervous irritation, telling upon an organ which is already somewhat disturbed in its functions, favor the development of the abnormal activity of that organ and the development of Graves' disease ?

What is very remarkable in the ordinary colloid goitre is that the specific thyroid tissue even in the most advanced colloid goitre still persists and is recognisable, despite the distension of the follicles ; the glandular tissue appears arrested in its function, but not destroyed. It is thus, anatomically speaking, within the bounds of possibility that such glandular substance should under altered conditions, take on active or over-active functions, and as a matter of fact, clinically, goitres with myxœdematous symptoms have been seen to develop into secondary Graves' disease.

6. Increased activity of the thyroid gland with hyperplasia and enlargement of the gland:—*Primary Graves' Disease* with accompanying enlargement without retention, and exophthalmos.

7. Relative or absolute increased activity of the thyroid gland without at first any recognisable enlargement of the organ:—*Formes Frustes of Graves' Disease.*

With reference to this part played by the relative or absolute increased secretion of the gland, I would refer to my previous paper upon the Internal Secretions which I gave at Washington in 1897.* I may here note that only recently my colleague, Dr. Armstrong, operated in the Montreal General Hospital upon a case which all recognised as one of definite Graves' disease, but when the thyroid gland was exposed, while it was of fair size, it certainly did not exceed in its dimensions what may be regarded as normal.

The above table, it will be seen, recognises that the essential cause

* Transactions of the Congress of American Physicians and Surgeons. Vol. IV., 1897, p. 103 and this JOURNAL, Vol. XXV., p. 856, 1897.

of Graves' disease is something apart from the essential cause of ordinary goitre, and that Graves' in itself primarily depends upon some nervous or other stimulus acting upon the thyroid gland and leading to increased activity and increased secretion. The sudden liberation of some of the retained secretion is best calculated to explain the paroxysmal disturbance of the "Graves'" type often met with in the course of ordinary simple goitre, as again does sudden increased discharge or absorption explain the disturbances seen in the course of Graves' disease itself, as well as the dangerous and sometimes fatal results following the operative handling of the diseased gland.

In the course of this short address I am unable fully to discuss the extraordinary variation which we come across in the histology of the goitrous thyroid—the degenerative and interstitial changes, the development of cysts (which in my laboratory at Montreal has been more especially studied by Dr. Bradley,*) the apparent and at times real hyperplasia of the gland, or again the development of actual malignant growth, whether carcinomatous or sarcomatous.

Nor again have I time to take up the vascular forms of goitre to which Virchow was the first to call prominent attention. These essentially vascular forms I have not come across; I have only noticed that in ordinary goitre there may be accompanying great vascularity. I can only suggest that the remarkable dilatation and enlargement of the arteries in the thyroid which Virchow so frequently met with, may in itself be an evidence of the obstruction to the perifollicular circulation brought about by the distention of the follicles. With regard to the cystic formation so frequently met with, I would point out that cysts in the thyroid having fluid contents are always of degenerative nature, and in the majority of cases follow localised hæmorrhage; as such they do not in themselves induce any of the generalised disturbances above mentioned, at most they case pressure symptoms. This has been very clearly pointed out by Dr. Shepherd.

Despite all the work that has been done of late years, the very multiplicity of the changes which occur makes it impossible to enter into a discussion as to the relative frequency of occurrence, and again as to the meaning of these various changes, nor again are we prepared to comprehend all of them. This much, however, may be said, that by far the commonest, in fact the common type, of ordinary goitre, is the colloid or parenchymatous. This form indeed must be taken as the type, and taking this as type, we can, if we regard it as essentially the result of obstruction and retention, gain some comprehension of the symptomatology of the condition.

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* Journal of Experimental Medicine, Vol. I., p. 401.